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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,154	09/20/2005	Margaretha Grind	056291-5256	1056

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EXAMINER	
AUDET, MAURY A	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
10/13/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,154	GRIND, MARGARETHA	
	Examiner	Art Unit	
	MAURY AUDET	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/2/10*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,16,19-21 and 54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,16,19-21 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/20/05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments and addition of new claim 54 is acknowledged. Applicant's arguments have been considered but are maintained for the reasons of record, as discussed below, including over new claim 54 (claiming general species of cholesterol treatment using the same compound).

The previous Office Action stated:

There are no amendments filed in this response over the outstanding 101 rejection, which his maintained. However, following a conference with Supervisor Jon Weber, the former Examiner's 35 USC 102 rejection has been brought back in, in the alternative against the outstanding 101 rejection. Thus, the present application had to be sent Non-Final. The previous arguments over the 102 rejection are no longer deemed persuasive based upon a renewed review of the claimed invention, under the broadest reasonable interpretation of the claims.

As indicated previously, the present application has been transferred from former Examiner Khanna to the present Examiner.

As stated previously, and maintained, it was not readily apparent what the real issue of the claimed invention was, based on the previous Examiner's approach to examining the claimed invention, via art under 35 USC 102. The art rejection however was not maintainable, at a minimum, in this Examiner's view, because of Applicant's expressly claimed limitation that a "cholesterol-lowering amount" of melagatran had to be administered. However, after further review, the real issue falls under 35 USC 101, Lack of Utility, as expounded on below.

Claim Rejections - 35 USC § 101-Maintained

The rejection of claims 14, 16, and 19-21 under 35 U.S.C. 101 because the claimed invention lacks patentable utility (or at a minimum a well established utility), is maintained for the reasons of record. Applicant's arguments have been considered but are not found persuasive. Applicant citing the specification, relies on a statement (citing Fig. 1 and 4) that as of the second month, marked mean differences were observed in treating cholesterol using ximelagatran. The Examiner is confused. Warfarin, as the Examiner indicated, is not known as a cholesterol-treating drug, follows the same trajectory for cholesterol levels as of the second month all the way to month 18. The Examiner is curious why Applicant didn't also file for the same claimed invention using Warfarin, since it also wasn't known to be useful for treating cholesterol, but followed the same exact trajectory for cholesterol levels, upon administration up to month 18?

However, since Warfarin, as Applicant admits on the record, is not known to be used for treating cholesterol. AND it followed the same cholesterol trajectory up to month 18, then Warfarin is merely a non-working control (e.g. like administering a placebo). And since ximelagatran followed the same trajectory, it worked no better than the control.

UNTIL, month 18? Where, yes - unexpectedly - the trajectory for cholesterol spiked rapidly for the next 3 months using ximelagatran and equally declined rapidly for Warfarin. This could be the only point of utility. However, no Dr. would recommend or Patient wait, 18 months for such a utility; when other drugs are known to work immediately to lower cholesterol. And since the paths of both agents mirrored each other up until month 18, the disparate paths of both agents taken for the next 3 months can only be viewed as an error; absent evidence to the contrary, which the Examiner did not find Applicant to address on the record.

The rejection is repeated below for continuity of record:

The below follows a thorough discussion of this case alongside Supervisor Jon Weber:

Specifically, the Examiner's rejection that the utility is not credible (the 3rd prong of 101), is maintained on the applied grounds, but based on different reasoning under this prong. Why would all of sudden 18 months after beginning therapy with a medication – and statistically significant results be found just 3 months later at month 21, when nothing happened in the previous 18? Did Applicant explore that maybe something else could have caused this? E.g. the diet those in the study were placed on, some other medication they were on (e.g. start of Lipitor, a known real world cholesterol lowering drug)? The are too many credibility questions that are unanswerable in this application, based on the data in the description/statistical models/controls in this study.

The analogy that the testing ground applied here was akin to testing Michael Jordan's utility as a baseball player against basketball players is ALSO maintained; however, is better suited under the 2nd prong of 101. Namely, the utility also is not "substantial". Substantial equates to "real world application/utility". Here, as Figures 1-4 show, Applicant – miraculously – had essentially NO RESULTS for ximelagatran lowering cholesterol until MONTH 18! No one – in the REAL WORLD application - would take a medication that required waiting 18 MONTHS for it to being working. Just as in the Examiner's analogy, no one would test Michael Jordan for his baseball skills in the commercial market (e.g. the professional level) by testing him against basketball players (e.g. test ximelogatran, a thrombin inhibitor, against a blood thinner, rather than also against well established cholesterol lowering agents, to test for it's real world application/utility).

The Examiner is very curious about one other fact. And believes Applicant's data mining for some use of ximelagatran, may have simply been an error or strongly questionable results. If this test was run for 12-26 months, as the specification indicates at page 20, variation step (d) that it was, why are e.g. cholesterol results for months 21-26 not shown in the Figures 1-4? Did cholesterol levels return to baseline after month 23? Or, was there only a few patients left IN THE STUDY AFTER MONTH 18 TO MONTH 21, IF the study e.g. stopped prior to month 17 for most of the 1700 patients in each study group, such that a representative # no longer existed? But, even if either alternative scenario doesn't apply, the odd results beginning at month 18-21 only, leaves open the question of whether some other UNcontrolled variable leaked into the patients regime that slightly impacted cholesterol panels, as opposed to anything xymelagatran did - since it hadn't done anything in the previous 18 months?

The rejection is repeated below for continuity of record:

The 3-prong test for whether a claimed invention has utility is that it must be specific, substantial, and credible. Here, the utility is deemed to be specific, questionably substantial, but fails as a credible utility, because the test data relied upon was run against a Non-Control - another compound (warfarin, also known as an anticoagulant) also not known to be a cholesterol-lowering agent, the asserted utility of the claimed invention.

Although Applicant has "asserted" a new "potential utility" (description page 18, last para) of melagatran as a cholesterol-lowering therapy and method thereof, the claimed invention is not in fact deemed to have utility for such or at a minimum a well established utility, based on the support within the description.

Thus the present 'potential utility' can only be deemed to be theoretical, at best, since the test was run against an agent that cannot be deemed a "control", warfarin, because the latter is not known to be a cholesterol-lowering agent.

[NOTE: A coextensive 35 USC 112 1st Enablement rejection has not be made, because technically Applicant's description provides that, at least in the comparison against warfarin, also having a known, established utility as an anticoagulant, the test data indicates that melagatran is arguably enabled to lower cholesterol MORE THAN it's similarly functioning warfarin].

The present description (page 18-20, Figures 1-4) has described test data showing melagatran lowers cholesterol more than the control, warfarin. However, the test is flawed, because warfarin is known or established to be a cholesterol-lowering agent and therefore cannot serve as a "control" for comparison.

As noted in Wikipedia, warfarin is known to be an anticoagulant (http://en.wikipedia.org/wiki/Warfarin, last modified on 20 September 2009):

Therapeutic uses

Warfarin is prescribed to people with an increased tendency for thrombosis or as secondary prophylaxis (prevention of further episodes) in those individuals that have already formed a blood clot (thrombus). Warfarin treatment can help prevent formation of future blood clots and help reduce the risk of embolism (migration of a thrombus to a spot where it blocks blood supply to a vital organ). Common clinical indications for warfarin use are atrial fibrillation, the presence of artificial heart valves, deep venous thrombosis, pulmonary embolism, antiphospholipid syndrome and, occasionally, after heart attacks (myocardial infarction).[10]

[Dosing]

In some countries, other coumadins are used instead of warfarin, such as acenocoumarol and phenprocoumon. These have a shorter (acenocoumarol) or longer (phenprocoumon) half-life, and are not completely interchangeable with warfarin. **The oral anticoagulant ximelagatran (trade name Exanta) was expected to replace warfarin to a large degree when introduced; however, reports of hepatotoxicity (liver damage)**

> prompted its manufacturer to withdraw it from further development. Other drugs offering the efficacy of warfarin without a need for monitoring, such as dabigatran and rivaroxaban, are under development.[12]

There is no public record/acknowledgement of warfarin's utility as a cholesterol-lowering agent.

Two references, additionally cited merely for illustration, indicate both melagatran and warfarin are known for having utility as anticoagulants, see Dugger, III (US 2003007729) claims 14, 37, 55, and 81; and Laughlin et al. (US 20050069527 A1) claim 55.

By analogy, the "potential utility" asserted by the test data of melagatran v. warfarin (a NON-control for study purposes), both anticoagulants and not known as cholesterol lowering agents, is the same "potential utility" that could have been asserted for Michael Jordan as a bona-fide Major League Baseball Player v. a control group of other NBA basketball players. Against other NBA players there is no doubt that Michael Jordan's stat's on the baseball diamond may have looked real good against other Non-Control NBA basketball players, if compared there against. However, when Michael Jordan was tested for his utility as a baseball player, against even Minor League Baseball Players, few of whom were at the quality of Major League Baseball Players, he was found even at this level to not have realistic utility as a Major League Baseball Player, with a batting ave. of somewhere between .185 - .220 only. His utility against real Control's at the Major League level, can only be presumed to have been less.

Michael Jordan put forth a specific and substantial desire to have utility as a Major League Baseball Player, but he was not found to be credible; credibly suited to have utility in MLB (as opposed to a few other cross-over athletes, who were able to establish their credibility against legitimate 'controls' at the AAA minor league level and Major League levels; such as

NBA basketball player Danny Ainge in the '70's/'80's and NFL football player Bo Jackson during the '80's/'90's).

Absent evidence to the contrary of further testing and data against actual cholesterol-lowering agents 'credible' as 'control's (beyond warfarin, a non-control anticoagulant), the presently claimed invention of melagatran as a cholesterol-lowering agent, is not deemed to have credible utility. And as such, would not be useful or find utility for such a purpose in the open market v. other cholesterol-lowering agents that have been tested against credible controls and found to be credibly useful therefor.

***Claim Rejections - 35 USC § 102*-Maintained as Reapplied**

The rejection of claims 14, 16, 19-21, and new claim 54, is maintained for the reasons of record. Applicant's arguments have been considered but are not found persuasive. Notwithstanding whether Applicant is able to show and/or maintain that his Fig. 1 and 2 show actual utility of melagatran for lowering cholesterol under 101 above; the 102 rejection is maintained that Gustaffson teach the use of melagatran for ischemic heart disease, and that the latter is a direct result of high cholesterol (e.g. pathway to ischemic heart disease). Thus, as Gustaffson showed reduction in ischemic heart disease based on the use of melagatran, Gustaffson was inherently treating, to some degree, effect on reducing cholesterol. **Absent evidence to the contrary by Applicant that melagatran does NOT affect cholesterol levels, and was somehow reducing ischemic heart disease through some other pathway.**

As the previous Examiner reasoned in line with two explanatory references (as opposed to 'relied upon', as this was not a 103 rejection), simply to illustrate the known ischemic heart

disease pathway not adequately explained in Gustaffson itself which is still maintained as based upon under the broadest reasonable interpretation of the claims:

Further evidence that the instantly claimed method of cholesterol-lowering therapy is not unobviously distinct from the method described by Gustafsson is based on a correlation between a therapy for lowering cholesterol in a patient which is associated with lowering the risk of ischemic heart disease described in "The Complete Drug Reference". On page 823, column 3, paragraph 5, "The Complete Drug Reference" **describes "Plasma-cholesterol concentrations of 5.2 mmol/litre (200 mg/dL) or less are associated with a low risk of ischaemic heart disease".** Additional evidence of the **correlation between a patient in need thereof of treatment for "ischemic heart disease" and one having "high cholesterol" is discussed by Kralova who teaches "In 114 patients there was a definite relation between the progressive phase of ischemic heart disease and high cholesterol .(I) level, which seemed to rise not only with the activity but also with the extent of vascular changes (abstract).**

The rejection is repeated below for continuity of record:

Even if Applicant chooses to argue over the 101, upon review of the original 102 rejection by the former Examiner (that was dropped when this Examiner inherited the application, based on a more narrow interpretation of the claims v. art); the Examiner (in conference with Supervisor Jon Weber) finds that the 102 does properly apply – and that Examiner's reasoning, Applicant's arguments thereafter no longer found persuasive - since the same compound was being administered to reduce the risk of cholesterol-based disorders, e.g. stroke (the pathway of how it really works not material, e.g. blood thinner v. anti-thrombin v. cholesterol lowering).

The rejection is repeated below for continuity of record:

5. (Maintained) Claim 14, 16, and 19-21 rejected under 35 U.S.C. 102(b) as being anticipated by Gustafsson D. (Astrazeneca; WO 02/36157) as evidenced by "The Complete Drug Reference" (as cited by the Applicant in the Remarks filed January 04, 2007) and Kralova (Vnitrni Lekarstvi (1963) 8:974-982).

The claims are drawn to a method of administering melagatran and prodrugs thereof to a patient in need of cholesterol-lowering therapy.

Applicant's argue that Gustafsson relates to the use of melagatran and its derivatives in the treatment of ischemic disorders in a patient having or at risk of atrial fibrillation (AF). Applicants contend that the present specification describes the patient population for the claimed therapy as being different from the population utilized by Gustafsson. Applicant's further argue that AF is distinct from cholesterol-based diseases by pointing to the "The Complete Drug Reference" which indicates differences in drug therapies for the different diseases, with thrombin inhibitors being preferred for patients with ischemic disorders.

Applicant's arguments have been considered but not found persuasive.

The Applicant's arguments are moot in view of Gustafsson's explicit disclosure (page 6, lines 1-10) that low molecular weight thrombin inhibitors, such as a prodrug of melagatran are acceptable for use in cholesterol-lowering therapy, which includes any therapy that results in beneficial modifications of serum profiles of total cholesterol, lipids, lipoproteins and apolipoproteins.

Further evidence that the instantly claimed method of cholesterol-lowering therapy is not unobviously distinct from the method described by Gustafsson is based on a correlation between a therapy for lowering cholesterol in a patient which is associated with lowering the risk of ischemic heart disease described in "The Complete Drug Reference". On page 823, column 3, paragraph 5, "The Complete Drug Reference" describes "Plasma-cholesterol concentrations of 5.2 mmol/litre (200 mg/dL) or less are associated with a low risk of ischaemic heart disease". Additional evidence of the correlation between a patient in need thereof of treatment for "ischemic heart disease" and one having "high cholesterol" is discussed by Kralova who teaches "In 114 patients there was a definite relation between the progressive phase of ischemic heart disease and high cholesterol .(I) level, which seemed to rise not only with the activity but also with the extent of vascular changes (abstract).

Final evidence is based on Applicant's admittance that the instant clinical trial protocol (Example 1) was similar in dosage, compound, and patient population (one having a history of AF and coronary heart disease, page 11, lines 1-20) to the one utilized by Gustafsson to demonstrate the effectiveness of the melagatran prodrug for the treatment of ischemic disorders.

Rejection is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MA, 10/12/10

/Maury Audet/
Primary Examiner, Art Unit 1654